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Hand hygiene for the prevention of infections in neonates (Protocol)

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[Intervention Protocol]

Hand hygiene for the prevention of infections in neonates

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To determine the effectiveness of different hand hygiene agents for preventing neonatal infections in community and health facility settings.

BACKGROUND

Annually, infections contribute to approximately 25% of the 2.8 million neonatal deaths worldwide; of those deaths, over 95% of sepsis-related neonatal deaths occur in low- and middle-income countries (Liu 2015). Neonatal infections may be acquired through exposure to the contaminated secretions of the birth canal or through contact with the contaminated environment (Chan 2013; Gebremedhin 2016; Schuchat 2000). Important environmental sources of infections for the neonate include the hands of the individuals who care for the many needs of the baby, including healthcare workers (HCWs) (Ram 2017; Rhee 2008). Contaminated hands play a major role in community-acquired and hospital-acquired neonatal infections, particularly among preterm infants, who are most susceptible. Community-based and health facility-based studies have suggested that hand washing may play preventive roles in neonatal infections in low-, middle-, and high-income countries (Herruzo-Cabrera 2001; Janota 2014; Rhee 2008).

Hand hygiene is an inexpensive and cost effective way of preventing neonatal infections, making it a practicable intervention in low- and middle-income settings (WHO 2009). Therefore, hand hygiene practices may hold strong prospects for reducing the occurrence of infections and for reducing infection-related neonatal deaths.

Description of the condition

The International Paediatric Sepsis Consensus Conference of 2005 defined neonatal sepsis as systemic inflammatory response syndrome in the presence of, or as a result of, suspected or proven infection in a neonate (Goldstein 2005). Neonatal sepsis is caused by a variety of micro-organisms including bacterial, viral, fungal, or rickettsial etiologies. Neonatal sepsis can be classified as early-onset (mainly acquired before or during delivery, or both) or late-onset neonatal sepsis (often acquired from exposure to contaminated environment). However, the age cut-off distinguishing early-

from late-onset neonatal sepsis ranges from 48 hours to 7 days (Haque 2007). Neonates are particularly susceptible to infections because of poor cutaneous and mucosal barrier mechanisms, poor macrophage function, poor opsonization, and low levels of serum immunoglobulins and complement (Cortese 2016; Wynn 2010). The susceptibility to neonatal infection is inversely related to the gestational age, with preterm neonates at higher risk of infections compared to term neonates (Afonso 2017).

Neonatal infections may lead to life-threatening multi-systemic morbidities such as shock, disseminated intravascular coagulopathies, cardiac failure, adrenal insufficiency, renal insufficiencies, and metabolic derangements (Cortese 2016; Goldstein 2005). Therefore, in spite of the availability of antibiotics and other adjunctive treatments, neonatal infections often lead to mortality accounting for a quarter of the global neonatal deaths (Liu 2015), prolonged hospital stay, early complications (Chu 2014), late complications (Adams-Chapman 2006), and huge economic burden (Ranjeva 2018).

The hands of mothers, other caregivers, and HCWs harbour significant microbial pathogens acquired during contact with patients or environmental surfaces (Aiello 2003). Contact of caregivers and HCW hands with respiratory secretions, diaper change, and direct skin contacts are often associated with transmission of infections to the newborn (Pessoa-Silva 2004). The average bacterial loads on the hands of caregivers (usually mothers) and neonatal intensive care nurses may be up to hundreds of thousands bacteria (Aiello 2003). This pattern of bacterial loads may vary among individuals but it is relatively constant for any individual (Aiello 2003; Larson 1998).

The World Health Organization (WHO) has described five steps of transmission of infections from person to person through the hands of HCWs. These steps are as follows:

- Organism being present in the skin of HCWs or object close to the patient.
- Organisms transferred to the hands of HCWs.
- Organisms survived in the hands of HCWs for several minutes.
- Hand washing or hand antisepsis by HCWs inadequate or completely omitted or HCWs use inappropriate agents for hand hygiene.
- Contaminated hands of HCWs come in contact with baby or object that will come in contact with babies (WHO 2009).

A number of organisms often found to contaminate the hands of caregivers include *Staphylococcus aureus*,*Klebsiella spp*,*Proteus mirabilis*, and *Actinobacter spp* and these are capable of causing infection in newborns (Cortese 2016; Herruzo-Cabrera 2001).

Description of the intervention

Hand hygiene refers to any form of hand cleansing. It is often used interchangeably with hand washing, which implies washing hands with plain or antimicrobial soap and water (WHO 2009). Hand hygiene also includes the use of various alcohol-based hand rubs, wipes, scrubs, and various antiseptic agents such as 0.5% chlorhexidine gluconate (CHG) (CADTH 2014), chlorine derivatives, iodine chloroxylenol (PCMX), quaternary ammonium compounds, and triclosan (WHO 2009). Hand washing is recommended to be performed before touching hospital equipment and instruments, before touching neonates, and in between cleaning and caring for neonates (Loveday 2014; WHO 2009).

How the intervention might work

Frequent and adequate hand hygiene by caregivers and HCWs may reduce neonatal infections by reducing dirt, organic materials, and microbial contaminations on the hands of these personnel, thereby reducing the risk of contamination of the babies and objects that come in contact with the babies (Herruzo-Cabrera 2001; Janota 2014; Won 2004).

Hand washing with water alone washes away dirt, but may not remove fats and oils on contaminated hands. This necessitates the use of soaps and detergents that have the capacity to dissolve fatty and hydrophobic materials to facilitate their subsequent removal with water (WHO 2009). Rotter 1999 reported that washing hands for 30 seconds reduced bacteria count to a greater extent than washing hands for 15 seconds.

Alcohol-based hand antiseptics and rubs have the ability to denature protein (Ali 2001). Alcohol-based preparations containing 60% to 80% alcohol have been reported to be most effective and safe (Ali 2001). Alcohols have been found to have excellent in vitro germicidal activity against both drug-susceptible and drug-resistant bacteria, *Mycobacterium tuberculosis*, some viruses, and fungi (Ali 2001; Herruzo-Cabrera 2001). Frequent use of appropriate alcohol-based hand rubs limits the spread of infections from the hands of HCWs to neonates (Herruzo-Cabrera 2001; Janota 2014).

Chlorhexidine solution attaches to and disrupts cytoplasmic membranes of pathogenic bacteria on the hands of HCWs thereby precipitating their cellular contents and resulting in cellular death (Rotter 1999). This action is similar to that of other hand antiseptic agents. Mortimer 1962 demonstrated that frequent hand hygiene with hexachlorophene antiseptic agents among nurses significantly reduced the risk of transmission of *Staphylococcus aureus* pathogens to babies admitted to the neonatal intensive care unit by these nurses compared to the nurses who did no hand washing or hand rubbing with the antiseptic agent. Hand hygiene has also been reported by several study investigators to reduce the rate and cross-transmission of pathogenic microbial agents, including methicillin-resistant *Staphylococcus aureus* strain (MRSA) in neonatal care units (Webster 1994; Zafar 1995).

Why it is important to do this review

Infections are a leading cause of death of neonates and children under five years of age globally (Liu 2015). Contaminated hands of mothers, other care givers, and HCWs, as well as hospital equipment are recognised as major sources of infections in the neonate (Aiello 2003; Pessoa-Silva 2004). Therefore, it is plausible that stringent hand hygiene practices in communities and health facilities may reduce the risk and incidence of neonatal infections and ultimately contribute to desired reduction in infection-related neonatal deaths.

Apart from contributing substantially to childhood deaths, neonatal infections often lead to prolonged hospital stay, early (Chu 2014) and late complications (Adams-Chapman 2006), and huge economic burden (Ranjeva 2018). A conservative estimate of the economic impact of neonatal sepsis in sub-Saharan Africa (SSA) revealed that 5.29 to 8.73 million DALYs are lost annually in the region to neonatal sepsis. This corresponds to an annual economic burden ranging from USD 10 billion to USD 469 billion in SSA alone (Ranjeva 2018). This huge economic cost may be reduced substantially with meticulous hand hygiene practices.

Hand washing practices may be a more efficient and cost-effective intervention aimed at reducing neonatal deaths for developing economies as the cost of procuring the required materials (soap and water and or alcohol rubs) may be negligible compared to the direct and indirect cost of taking care of morbidities associated with neonatal infections (WHO 2009). Hand washing may also be more psychologically satisfying and thus, more acceptable for families compared to more technologically-advanced preventive measures (Greenland 2013; WHO 2009), A priority-setting exercise that involved stakeholders from Anglophone West African countries identified this review question as very important (Effa 2017), However, there is no high-quality systematic review to show the effectiveness of hand hygiene in the prevention of neonatal infections and the associated morbidities and deaths.

The United Nations, through global goals termed "the Sustainable Development Goals" (SDGs), aims to end preventable deaths of newborns and children under five years of age by 2030, among other lofty goals (UN 2017). The third goal of the 17 SDGs cannot be achieved without reducing neonatal mortality, and one possible way of achieving this is to substantially reduce infection-related neonatal mortality in low- and middle-income countries (UN 2017). Meticulous hand hygiene may reduce these preventable deaths of newborns.

OBJECTIVES

To determine the effectiveness of different hand hygiene agents for preventing neonatal infections in community and health facility settings.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs), cluster-RCTs, and quasi-RCTs.

Types of participants

Participants will include those who received the interventions (pregnant women, mothers, other care givers, and HCWs) within the community or in health facility settings. For the purpose of this Cochrane Review we define the community setting as any setting other than a healthcare facility.

Source of the outcome data: neonates (aged from birth to 28 days of life).

Types of interventions

We will include studies that compare any of the following interventions or in combination to any of the comparisons.

Intervention and comparison

- Hand washing with soap and water versus no intervention.
- Alcohol-based hand rub/hand sanitiser versus no intervention.
- Hand washing and alcohol-based hand rub/hand sanitiser versus no intervention.
- Hand washing with soap and water versus alcohol-based hand rub/hand sanitiser.
- Comparison of different alcohol-based hand rub/hand sanitisers (e.g. rubs, wipes, scrubs, CHG, chlorine derivatives, PCMX, quaternary ammonium compounds, and triclosan).

Types of outcome measures

Primary outcomes

- Incidence of (author-defined) suspected infections within the first 28 days of life.
- Incidence of bacteriologically confirmed infections (types of infection as specified by authors) within the first 28 days of life.
- All-cause mortality within the first seven day of life (early neonatal death).
- All-cause mortality from the 8^{th} to 28^{th} day of life (late neonatal death).

Secondary outcomes

- Duration of hospital stay.
- Any hospitalisation for neonates managed at the community setting.
- Incidence of community-acquired and hospital-acquired infections.
- Author-reported adverse events, such as skin changes and reactions to hand wash and rubs.

Search methods for identification of studies

We will contact Cochrane Neonatal's Information Specialist to assist us with the electronic search. We will use the criteria and standard methods of Cochrane and Cochrane Neonatal (see the Cochrane Neonatal search strategy for specialized register). We will search for errata or retractions from included studies published in full-text on PubMed (www.ncbi.nlm.nih.gov/pubmed), and will report the date this was done in the review.

Electronic searches

We will conduct a comprehensive search including: Cochrane Central Register of Controlled Trials (CENTRAL, current issue) in the Cochrane Library; MEDLINE via Ovid (1946 to present); PubMed (for the previous year); Embase via Ovid (1974 to present); and CINAHL via EBSCO host (1981 to present). We will use Cochrane Neonatal's standard search strategy for neonates and RCTs (Appendix 1), in combination with terms for hand hygiene. The full MEDLINE search strategy is available in Appendix 1 and will be adapted to suit the other databases. We will not apply language restrictions.

We will search clinical trials registries for ongoing or recently completed trials, including ClinicalTrials.gov (clinicaltrials.gov); the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en/), and the ISRCTN Registry (www.isrctn.com/).

Searching other resources

We will also search the reference lists of any articles selected for inclusion in this review in order to identify additional relevant articles. We will search the proceedings of the annual meetings of the Paediatric Academic Societies (1993 to present), the European Society for Paediatric Research (1995 to present), the Royal College of Paediatrics and Child Health (2000 to present), and the Perinatal Society of Australia and New Zealand (2000 to present). Trials reported only as abstracts will be eligible if sufficient information is available from the report or from contact with the study authors to fulfil the inclusion criteria.

Data collection and analysis

Selection of studies

Two review authors (BPK and TAO) will independently assess the eligibility of the results of literature search for potentially relevant trials. The two review authors will assess the full reports of the potentially relevant trials, and independently determine if they met the inclusion criteria using a pre-tested eligibility form. Where there are disagreements on study eligibility, a third review author (OO) will resolve it. We will list all studies excluded after full-text assessment, along with the reasons for excluding them, in a 'Characteristics of excluded studies' table. We will ensure that trials with multiple publications are included only once, and where the multiple publications included different but relevant outcomes, we will include all publications of the same trial as one study in the review.

We will record the selection process in sufficient detail to complete a PRISMA flow diagram (Moher 2009).

Data extraction and management

Two review authors (BPK and CO) will independently extract data from the included studies using a pre-tested data extraction form. One review author (OO) will enter the extracted data into Review Manager 5 (RevMan 5) (Review Manager 2014), Cochrane's review writing software, while another author (TAO) will cross-check the data for completeness and accuracy. We will extract data on the number of participants randomised and the number analysed in each group for each reported outcome.

For continuous outcomes, we will extract the number of participants for each treatment arm, arithmetic means, and standard deviations (SDs). We will extract data on reported adverse events as dichotomous outcomes.

We will attempt to contact the trial authors for additional information on missing or unclear data.

Assessment of risk of bias in included studies

Two review authors (BPK and CO) will independently assess the risk of bias (low, high, or unclear) of all included trials using the Cochrane 'Risk of bias' tool (Higgins 2017) for the following domains:

- Sequence generation (selection bias).
- Allocation concealment (selection bias).
- Blinding of participants and personnel (performance bias).
- Blinding of outcome assessment (detection bias).
- Incomplete outcome data (attrition bias).
- Selective reporting (reporting bias).
- Any other bias.

We will resolve any disagreements by discussion or by consulting a third review author (OO). See Appendix 2 for a more detailed description of risk of bias for each domain.

Measures of treatment effect

The type of treatment effect used in describing each of the listed outcomes will be dependent on the type of data extracted for the specific outcome. For continuous data, we will report the mean difference (MD) for continuous outcomes. We will present all measures of effect with their corresponding 95% confidence intervaI (CI). We will extract post-intervention values and will utilise the mean and SD values for the analysis. For binary data, we will analyse binary outcomes by calculating the risk ratio (RR) and risk difference (RD) with 95% CIs.

Unit of analysis issues

For studies that are cluster-RCTs, we will extract results that have been adjusted for clustering. Where adjustment is not made for clustering, we plan to adjust the results for clustering by multiplying the standard errors of the treatment effect by the square root of the design effect. We will calculate the design effect as 1+(m-1)*ICC where 'm' is the average cluster size and ICC is the ICC coefficient (Higgins 2011). Where ICC is not reported, we plan to estimate the ICC from other trials included in the review or by contacting trial investigators. If we cannot adjust results for clustering, we will not combine the results in meta-analyses with individual RCTs or cluster-adjusted RCTs but will present results in an additional table. We expect most studies will report results for our prespecified time-points (which are early neonatal period (first seven days of life); late neonatal period (8^{th} to 28^{th} day of life), and duration of hospital stay), irrespective of whether randomisation is at individual level or in cluster. To avoid unit of analysis error due to meta-analysis of results from several time-points, we will select a maximum of three most clinically important time-points (as reported by the authors of included studies) for each outcome.

Dealing with missing data

We plan to perform the analysis according to the intention-to-treat principle (all randomised participants will be analysed in the groups to which they were originally assigned) if the authors of included studies account for all randomised participants. We will consider missing data greater than 10% as too much missing data. We will perform an 'as treated analysis' using data of those participants who completed the study and an 'intention to treat analysis' by analysing participants in the group to which they were randomised, irrespective of whether they completed the study or not. We will compare the two results and use the result that is most representative of the true effect. We will attempt to contact trial authors for missing or incomplete data. Where this is not feasible, we will employ a complete-case analysis, such that we will exclude participants for whom no outcome is reported from the analysis, if we judge the study to be at low risk of bias regarding allocation sequence generation and allocation concealment. This analysis assumes that the patients for whom an outcome is available are representative of the original randomised patients (Higgins 2011).

Assessment of heterogeneity

We will assess statistical heterogeneity between subgroups by visually inspecting the forest plots for overlapping CIs, applying the Chi^2 test (where a P value < 0.10 is considered statistically significant), and by using the I^2 statistic (statistic (with values < 25% representing no heterogeneity; 25% to 49% low; 50% to 74% representing moderate heterogeneity; and $\geq$ 75% substantially high heterogeneity).

Assessment of reporting biases

We plan to explore publication biases by constructing a funnel plot, provided a sufficient number of trials contribute to the treatment comparison.

Data synthesis

We will analyse the data using Review Manager 5 (Review Manager 2014). In the first instance, we will apply a fixed-effect meta-analysis. However, if we detect moderate heterogeneity but still consider it appropriate to combine the trials, we will then use a random-effects approach. Where heterogeneity is very high such that meta-analysis is not appropriate, we will not display the results in forest plots. We will present the results as narrative and downgrade the quality of the evidence for inconsistency and will display results in a 'Summary of findings' table.

We will stratify the analyses by when the outcome is measured (post-intervention). We will stratify by difference in mean of pre- and post-intervention. We will also analyse pair-wise comparison of 'handwashing with soap and water' versus 'alcohol/antiseptic hand rubs', 'handwashing with soap and water' versus 'no intervention', 'alcohol/antiseptic hand rubs' versus 'no intervention', and 'one class of alcohol/antiseptic hand rubs' versus 'other class of alcohol/antiseptic hand rubs' using mean and standard deviation values. We will also use risk ratio (RR), RD (and number needed to treat (NNT)/number needed to harm (NNH) when RD is significant), and weighted mean difference (WMD), all with 95% CIs. We will place cluster-RCTs on separate forest plots from trials that randomise individual patients if the cluster-RCTs are not adjusted for clustering.

We will present the main results of the review alongside a GRADE appraisal of the quality of the evidence in the 'Summary of findings' tables.

Quality of the evidence

We will use the GRADE approach, as outlined in the GRADE Handbook (Schünemann 2013), to assess the quality of the evidence for the following (clinically relevant) outcomes:

- Incidence of bacteriologically confirmed infections within the first 28 days of life.
- Incidence of suspected infections within the first 28 days of life.
- Infection-related mortality within the first 28 days of life.
- Adverse events.
- Duration of hospitalisation.
- Acceptability of hand washing practices by mothers and care givers.

Two review authors will independently assess the quality of the evidence for each of the outcomes above. We will consider evidence from RCTs as high quality, but will downgrade the quality of the evidence by one level for serious (or two levels for very serious) limitations based upon the following: design (risk of bias), consistency across studies, directness of the evidence, precision of estimates, and presence of publication bias. We will use the GRADEpro Guideline Development Tool to create a 'Summary of findings' table to report the quality of the evidence (GRADEpro GDT 2015).

The GRADE approach results in an assessment of the quality of a body of evidence in one of four grades:

- High: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
- Very low: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Subgroup analysis and investigation of heterogeneity

If there is significant heterogeneity in the meta-analysis, we will investigate the possible causes using subgroup analyses. Where feasible, subgroups will include geographical region (low- and middle-income countries versus high-income countries), babies' gestational age (preterm versus term), setting (community-based studies versus health facility-based studies), and onset of infection (early- or late-onset neonatal sepsis).

We will perform a subgroup analysis of different alcohol-based hand rub/hand sanitiser (e.g. rubs, wipes, scrubs, CHG, chlorine derivatives, PCMX, quaternary ammonium compounds, and triclosan).

Sensitivity analysis

We will conduct a sensitivity analysis to investigate the robustness of the results to the risk of bias components by including only trials at low risk of bias if 10 studies or more meet the inclusion criteria of the review. We will also conduct sensitivity analyses to investigate the robustness of our meta-analysis by excluding cluster RCTs with imputed ICC from another trial from the analysis.

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The Methods section of this protocol is based on a standard template used by Cochrane Neonatal.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Cochrane Neonatal standard search strategy

PubMed

((infant, newborn[MeSH] OR newborn*[TIAB] OR "new born"[TIAB] OR "new borns"[TIAB] OR "newly born"[TIAB] OR baby*[TIAB] OR babies[TIAB] OR premature[TIAB] OR prematurity[TIAB] OR preterm[TIAB] OR "pre term"[TIAB] OR "low birth weight"[TIAB] OR "low birthweight"[TIAB] OR VLBW[TIAB] OR LBW[TIAB] OR infant[TIAB] OR infants[TIAB] OR infantile[TIAB] OR infancy[TIAB] OR neonat*[TIAB]) AND (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) NOT (animals[mh] NOT humans[mh]))

MEDLINE via Ovid

1. exp infant, newborn/
2. (newborn* or new born or new borns or newly born or baby* or babies or premature or prematurity or preterm or pre term or low birth weight or low birthweight or VLBW or LBW or infant or infants or infantile or infancy or neonat*).ti,ab.
3. 1 or 2
4. randomized controlled trial.pt.
5. controlled clinical trial.pt.
6. randomized.ab.
7. placebo.ab.
8. drug therapy.fs.
9. randomly.ab.
10. trial.ab.
11. groups.ab.
12. or/4-11
13. exp animals/ not humans.sh.
14. 12 not 13
15. 3 and 14

Embase via Ovid

1. exp prematurity/
2. exp infant/
3. (newborn* or new born or new borns or newly born or baby* or babies or premature or prematurity or preterm or pre term or low birth weight or low birthweight or VLBW or LBW or infant or infants or infantile or infancy or neonat*).ti,ab.
4. 1 or 2 or 3
5. (human not animal).mp.
6. (randomized controlled trial or controlled clinical trial or randomized or placebo or clinical trials as topic or randomly or trial or clinical trial).mp.
7. 4 and 5 and 6

CINAHL

(infant or infants or infantile or infancy or newborn* or "new born" or "new borns" or "newly born" or neonat* or baby* or babies or premature or prematures or prematurity or preterm or preterms or "pre term" or premies or "low birth weight" or "low birthweight" or VLBW or LBW) AND (randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR clinical trials as topic OR randomly OR trial OR PT clinical trial)

Cochrane Library

(infant or infants or infantile or infancy or newborn* or "new born" or "new borns" or "newly born" or neonat* or baby* or babies or premature or prematures or prematurity or preterm or preterms or "pre term" or premies or "low birth weight" or "low birthweight" or VLBW or LBW or ELBW or NICU)

MEDLINE search strategy

1. exp Hand Hygiene/
2. exp Hand Disinfection/
3. (handwash* or handrub*).mp.
4. (hand* adj2 (clean* or decontaminat* or disinfect* or hygiene or hygienic* or saniti* or sterili* or wash* or scrub* or alcohol* or antisep* or disinfect* or rub* or aseps* or aseptic* or wipe* or chlorhexidine or triclosan or soap*)).mp.
5. (hand* adj2 chlorine derivative*).mp.
6. (hand* adj2 iodine chloroxylenol).mp.
7. (hand* adj2 quaternary ammonium compound*).mp.
8. (scrub* adj2 surgical).mp.
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. exp HAND/
11. hand*.tw,kf.
12. 10 or 11
13. exp Bacterial Infections/pc [Prevention & Control]
14. exp Cross Infection/pc [Prevention & Control]
15. exp HYGIENE/
16. exp Infection Control/
17. exp DISINFECTANTS/
18. exp SOLUTIONS/
19. exp ALCOHOLS/
20. exp Anti-Infective Agents, Local/
21. exp SOAPS/
22. exp ANTISEPSIS/
23. exp DISINFECTION/
24. exp STERILIZATION/
25. exp CHLORHEXIDINE/
26. exp TRICLOSAN/
27. exp Quaternary Ammonium Compounds/
28. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27
29. 12 and 28
30. 9 or 29
31. exp infant, newborn/
32. (newborn* or new born or new borns or newly born or baby* or babies or premature or prematurity or preterm or pre term or low birth weight or low birthweight or VLBW or LBW or infant or infants or infantile or infancy or neonat*).ti,ab.
33. 31 or 32
34. randomized controlled trial.pt.
35. controlled clinical trial.pt.
36. randomized.ab.
37. placebo.ab.
38. drug therapy.fs.
39. randomly.ab.
40. trial.ab.
41. groups.ab.
42. or/34-41
43. exp animals/ not humans.sh.
44. 42 not 43

45. 33 and 44
46. 30 and 45

Appendix 2. Risk of bias tool

We will use the standard methods of Cochrane and Cochrane Neonatal to assess the methodological quality of the trials. For each trial, we will seek information regarding the method of randomisation, blinding, and reporting of all outcomes of all the infants enrolled in the trial. We will assess each criterion as being at a low, high, or unclear risk of bias. Two review authors will separately assess each study. We will resolve any disagreement by discussion. We will add this information to the 'Characteristics of included studies' table. We will evaluate the following issues and enter the findings into the 'Risk of bias' table.

1. Sequence generation (checking for possible selection bias). Was the allocation sequence adequately generated?

For each included study, we will categorise the method used to generate the allocation sequence as:

- low risk (any truly random process e.g. random number table; computer random number generator);
- high risk (any non-random process e.g. odd or even date of birth; hospital or clinic record number); or
- unclear risk.

2. Allocation concealment (checking for possible selection bias). Was allocation adequately concealed?

For each included study, we will categorise the method used to conceal the allocation sequence as:

- low risk (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth); or
- unclear risk.

3. Blinding of participants and personnel (checking for possible performance bias). Was knowledge of the allocated intervention adequately prevented during the study?

For each included study, we will categorise the methods used to blind study participants and personnel from knowledge of which intervention a participant received. Blinding will be assessed separately for different outcomes or class of outcomes. We will categorise the methods as:

- low risk, high risk, or unclear risk for participants; and
- low risk, high risk, or unclear risk for personnel.

4. Blinding of outcome assessment (checking for possible detection bias). Was knowledge of the allocated intervention adequately prevented at the time of outcome assessment?

For each included study, we will categorise the methods used to blind outcome assessment. Blinding will be assessed separately for different outcomes or class of outcomes. We will categorise the methods as:

- low risk for outcome assessors;
- high risk for outcome assessors; or
- unclear risk for outcome assessors.

5. Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations). Were incomplete outcome data adequately addressed?

For each included study and for each outcome, we will describe the completeness of data including attrition and exclusions from the analysis. We will note whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information is reported or supplied by the trial authors, we will re-include missing data in the analyses. We will categorise the methods as:

- low risk (< 20% missing data);

- high risk (≥ 20% missing data); or
- unclear risk.

6. Selective reporting bias. Are reports of the study free of suggestion of selective outcome reporting?

For each included study, we will describe how we investigated the possibility of selective outcome reporting bias and what we found. For studies in which study protocols were published in advance, we will compare prespecified outcomes versus outcomes eventually reported in the published results. If the study protocol was not published in advance, we will contact study authors to gain access to the study protocol. We will assess the methods as:

- low risk (where it is clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported);
- high risk (where not all the study's prespecified outcomes have been reported; one or more reported primary outcomes were not prespecified outcomes of interest and are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported); or
- unclear risk.

7. Other sources of bias. Was the study apparently free of other problems that could put it at a high risk of bias?

For each included study, we will describe any important concerns we have about other possible sources of bias (for example, whether there was a potential source of bias related to the specific study design or whether the trial was stopped early due to some data-dependent process). We will assess whether each study was free of other problems that could put it at risk of bias as:

- low risk;
- high risk;
- unclear risk

If needed, we plan to explore the impact of the level of bias through undertaking sensitivity analyses.

CONTRIBUTIONS OF AUTHORS

All review authors contributed to the concept and the design of the protocol. Bankole Peter Kuti (BPK) and Tinuade A Ogunlesi (TAO) developed the first draft of the protocol. Olabisi Oduwole (OO) wrote the Methods section of the protocol. We prepared and developed this protocol under the guidance of Martin M Meremikwu (MM). All review authors critically appraised and approved the final protocol draft.

DECLARATIONS OF INTEREST

BPK has no conflicts to declare.

TAO has no conflicts to declare.

OO has no conflicts to declare.

CO has no conflicts to declare.

EU has no conflicts to declare.

MM has no conflicts to declare.

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